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On January 2, 2001

TOWNSEND and TOWNSEND and CREW LLP

By: Paula Daniels Hunley

PATENT
Attorney Docket No.: 15270-004300US
Client Reference No.: 00188-US-NEW

Declaration

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Philip Gambel
S. A. Rubin et al.	Art Unit: 1644
Application No.: 09/010,377	
Filed: January 21, 1998	
For: TREATMENT OF VIRAL ENCEPHALITIS BY AGENTS BLOCKING ALPHA-VLA-4 INTEGRIN FUNCTION	DECLARATION OF STEPHEN B. FREEDMAN UNDER 37 CFR § 1.132

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Stephen B. Freedman, state as follows:

1. I am Vice President, Drug Discovery, at Elan Pharmaceuticals, Inc. A copy of my curriculum vitae is attached.

2. I have reviewed the above application and the outstanding office action. The application has claims directed to methods of treating viral encephalitis in a patient that is free of multiple sclerosis using an agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen α4 integrin. I understand that the Examiner agrees that these claims

are enabled for antibodies directed to the α4 subunit of VLA-4 and peptide agents having the formula set forth in SEQ ID NOs: 3-5 in the specification of the subject application. However, I understand the Examiner believes that undue experimentation might have been required to identify other agents suitable for use in the methods at the priority date of the subject invention, which I understand to be January 21, 1998. In light of the facts discussed below, I respectfully disagree with this view.

3. The activity demanded of agents for use in the presently claimed methods is a simple one, that is, the agents should inhibit leukocyte binding to brain endothelial cells via leukocyte surface antigen α4 integrin. As described at page 8 of the specification, such inhibitory activity can be assayed by, for example, detecting the existence or strength of binding of an agent to cells bearing α4 integrin or VCAM-1. The agents can also be tested by determining capacity of an agent to inhibit binding of leukocytes to inflamed endothelial cells (or cells bearing a VCAM-1 counterreceptor, or purified VCAM-1 counterreceptor). These assays can be used to identify not only antibodies against α4 integrin, but also other agents that inhibit leukocyte binding to brain endothelial cells via α4 integrin including antibodies to VCAM-1 and nonantibody agents binding to either α4 integrin or VCAM-1. Such screening methods can easily be performed as a high throughput assay, for example, in a 96-well format. Use of high through put assays to screen receptor binding interactions was routinely performed in the art at the priority date of the subject invention (see, e.g., Horuk et al., *J. Immunol. Methods* 119, 255-258 (1989); Woof & Burton, *J. Immunol. Methods* 111, 205-207 (1988); and Slack et al., *Biotechniques* 7, 1132-1138 (1989)) (copies attached as Exhibits A, B, and C, respectively).

4. Production of a repertoire of antibodies to VCAM-1 for screening by the above approach presented no particular difficulties at the priority date of the subject invention. VCAM-1 had been cloned and expressed before the priority date of the invention (Osborne et al., *Cell* 59, 1203-1211 (1989)) (copy attached as Exhibit D). Given the existence of a cloned source, and therefore relatively large amounts of VCAM-1, the remaining steps of immunizing an animal and isolating hybridomas would have been routine. To illustrate, several monoclonal antibodies to VCAM-1 were reported to have been made prior to the priority date of the subject

invention. See, e.g., Hadasit Medical Res. Services & Dev, WO 95/30439; Carlos et al., *Blood* 76, 965-970 (1990); Dore-Duffy et al., *Frontiers in Cerebral Vascular Biology: Transport and Its Regulation*, pp. 243-248 (Eds. Drewes & Betz, Plenum, NY 1993); Baron et al., *J. Exp. Med.* 177, 57-68 (1993); and WO 95/30439 (copies attached as Exhibits E, F, G, H, and I, respectively). The latter two antibodies were reported to block VCAM-1 binding to VLA-4. Further, Baron et al. report that antibodies to VCAM-1 and VLA-4 had the "same effect" in delaying onset of disease in an EAE model of multiple sclerosis (see p. 63, column 1).

5. Given the existence of a repertoire of antibodies to VCAM-1 and of the above assays for screening them, I believe it would have been a routine matter to identify a subset of antibodies to VCAM-1 with the desired property of inhibiting leukocyte binding to brain endothelial cells via leukocyte surface antigen α4 integrin. The principles of screening for such antibodies are analogous to those used to screen antibodies to α4 integrin. Just as it would have been routine to identify α4 integrin antibodies that inhibit leukocyte binding to brain endothelial cells via α4 integrin, so too would it have been routine to identify suitable antibodies to VCAM-1 that inhibit leukocyte binding to brain endothelial cells via α4 integrin.

6. In my view, it would also have been a routine matter to identify nonantibody agents that inhibit leukocyte binding to brain endothelial cells via α4 integrin. A large number of candidate molecules were available for screening at the priority date of the subject invention. Such molecules include peptide mimetics of α4 integrin or VCAM-1 and antibodies binding thereto, members of combinatorial libraries, as well as large numbers of small organic molecules and natural products that were available for drug screening. Combinatorial approaches for generating large libraries include the phage display method discussed by Ladner, WO 90/02809 (copy attached as Exhibit J) allows production of large polypeptide libraries (e.g., at least 10^8 members). The libraries are contacted with a target and screened by affinity selection for binding to the target. In the present situation, the target would be, for example, VCAM-1 or α4 integrin, and the phage library would be screened for binding to one of these targets, optionally in competition with α4 integrin or VCAM-1, respectively.

7. Another mass screening procedure that is applicable both to peptides and other molecules synthesizable in a step-by-step fashion is termed VLSIPS™ (WO 90/15070) (copy attached as Exhibit K). In this method, synthetic steps occur in cells of a substrate activated by photolithography, resulting in generation of large libraries of compounds attached at known positions on the substrate. The compounds are then screened for binding to a labeled receptor. The position, and hence the identity, of compounds that bind to their receptor is revealed from the location of label. In this and other mass screening techniques, the presence of the desired activity in molecules identified by mass screening techniques can be confirmed in the same assays that were used to identify the α4 integrin antibodies for use in the presently claimed methods.

8. Experience has shown that screening of libraries of peptides or other compounds can typically identify library members having specific affinity for a given target without any prior knowledge of molecular structure needed for binding. Examples of diverse agents that can be screened to identify compounds that bind to α4 integrin and block its binding to VCAM-1 are reported by WO 96/22966 (copy attached as Exhibit L). Likewise, several small molecules that bind to VCAM-1 and inhibit its interaction with VLA-4 have been reported. See, e.g., WO 96/31206 (copy attached as Exhibit M). The diversity of molecular structures of compounds that inhibit binding of VLA-4 to VCAM-1 shows that suitable compounds can be isolated without prior knowledge of structural requirements.

9. For these reasons, I conclude that it would also have been a routine matter to isolate nonantibody agents that block leukocyte binding to brain endothelial cells via α4 integrin at the priority date of the subject application.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 7th December 2000 By Stephen Freedman
Stephen B. Freedman

Attachments: curriculum vitae; Exhibits A-M.
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